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09/762,602	03/21/2001	Petros Karouzakis	1581/128WO	6697

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/762,602	Applicant(s) KAROUZAKIS ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 21, 2002 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In addition, claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cyclodextrin, does not reasonably provide enablement for other agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines "an agent having beneficial effects". There is no biochemical, physical, or structural criteria provided in the specification to define what the agents might be. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "agent having beneficial effects" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "agent having beneficial effects", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-33, 43, 44, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 recites the limitation "an agent" in line 1. It is unclear what compounds are encompassed by the claims.

The expression "for achieving a beneficial effect in women..." in claim 43 renders the claim indefinite. "Beneficial" is a relative term. It is unclear what effects may be considered beneficial to a host encompassed by the claims.

The expression "erectile dysfunction" in claims 32 and 34 renders the claims indefinite because female subjects should not have erectile dysfunction.

Claims 44 and 46 recite the limitation "A pharmaceutical composition according to claim 41" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Response to arguments

Applicant's rebuttal arguments averring the beneficial effects were disclosed in the specification of page 6, line 15 have been considered but are not found persuasive. It is not clear what agents and beneficial effects disclosed. Only a few examples of the agents are disclosed. It is also not clear as to what effect(s) is(are) considered "beneficial" to the patients encompassed thereby. Can it be financially beneficial?

Therapeutically beneficial? Mentally or emotionally beneficial? The metes and bounds of the claims are not defined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Alam et al. (US Patent 5,252,602 from the IDS received October 21, 2002).

Alam et al. teaches a method of using a topical misoprostol composition in an amount of 200μg to about 5mg (See claim 9).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowrey (US Patent 5,981,563), Neal (US Patent 6,103,765), Nahoum (US Patent 5,773,457) and Buyuktimkin et al. (US Patent 6,046,244) in view of El-Rashidy (US

Patent 5,256,652), and Reilly (chapter 80 in Remington: The Science and Practice of Pharmacy, page 1397, 1509-1512), references of record in the previous office action.

Lowrey teaches that the sexual response in females involve vasodilation and engorgement of the genitalia with arterial blood in a manner analogous to the male erectile response (See col. 5, line 38-51). Lowery further teaches that vasodilators facilitate increase blood flow to the genitalia is useful as modulating female sexual response (See col. 17, line 22-52).

Neal teaches misoprostol and alprostadil are known and preferred vasodilating agents for treating male sexual dysfunction (See col. 3, line 48-52).

Nahoum teaches that both misoprostol (a prostaglandin E_1 analog) and alprostadil (a prostaglandin E_1), among other vasoactive agents, are useful in treating female sexual dysfunction (See col. 9, lines 47-48; lines 53- col.10, line 1). Nahoum also teaches that the female sexual dysfunction treating composition, which may contain misoprostol, can be administered topically as gel, cream or ointment (See particularly col. 10, line 48-49). Nahoum also teaches that penetration enhancing agent may be incorporate into the female sexual dysfunction treating composition, which may contain misoprostol (See col. 14, line 8 - col. 15, line 48).

Buyuktimkin et al. teaches that a topical prostaglandin E_1 (PGE_1 also known as alprostadil) composition, which has penetration enhancer composition in it, is useful for treating any disease that is treated by prostaglandin E_1 (see col.1, line 27-28 and col. 8, line 6-8). Buyuktimkin et al. also teaches the amount of the active prostaglandin ingredient to be 0.1-0.5 %w/v (See col. 10, Table 1).

The primary references do not expressly teach that the topical sexual dsyfunction treating composition employs misoprostol or misoprostol and alprostadil in combination particularly. The primary references do not expressly teach that the amount of misoprostol to be 0.3-0.9%. The primary references do not expressly teach the application of the topical prostaglandin composition in a method of treating female sexual dysfuntion to the vagina or clitoris. The primary references do not expressly teach the female sexual dsyfunction treating method comprising α-cyclodextrin, gelatin, and hydroxymethylcellulose. The primary references do not expressly teach the female sexual dsyfunction treating method comprising hydroxypropyl methylcellulose which comprises hydroxypropyl methylcellulose 3000 in the amount of 4% w/v.

El-Rashidy teaches a topical sexual dysfunction treating composition that comprises a vasodilating agent, α-cyclodextrin, and hydroxypropyl methylcellulose (See col. 3, line 67-68; col. 6, line 2-4). El-Rashidy also teaches that the amount of hydroxypropyl methylcellulose is 2-3%w/v (See col.8, Table II).

Reilly teaches that gelatin is useful as an emulsifying agent utilized to formulate topical formulation (page 1397, col. 1; also page 1510 col.1, last paragraph).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a topical female sexual dysfunction treating composition of misoprostol in the amount of 0.3-0.9% with or without the second vasoactive agent onto the vagina or clitoris. It would have been obvious for one of ordinary skill in the art at the time the invention was made to incorporate α-cyclodextrin, gelatin, and hydroxyproopyl methylcellulose, which comprises hydroxypropyl methylcellulose 3000 in the amount of

4%, into the topical female sexual dysfunction treating composition in a method to treat female sexual dysfunction.

One of ordinary skill in the art would have been motivated to apply the sexual dsyfunction treating composition, employing misoprostol in the amount of 0.3-0.9%, with or without another vasodilator, cyclodextrin, gelatin, and hydroxypropyl methylcellulose, which comprises hydroxypropyl methylcellulose 3000 in the amount of 4%, onto the vagina or clitoris in a method to treat female sexual dysfunction. Vasoactive agents are known to be useful to modulate female sexual response and treat female sexual dysfunction thereby, very much in the same way as male sexual dysfunction. Furthermore, misoprostol and prostaglandin E_1(alprostadil) are known to be vasodilating agents and have been used as preferred vasoactive agents for male sexual dysfunction. Therefore, employing known vasodilating agents, such as misoprostol and alprostadil specifically, in the treatment of female sexual dysfunctions would be reasonably expected to be effective, absent evidence to the contrary. In addition, topical formulation of alprostadil is known, substituting or incorporating misoprostol into such topical formulation of Buyuktimkin et al. would be reasonably expected to be effective in treating female sexual dysfunction.

Moreover, it is known in the art that increasing female sexual response is associated with vasodilation and engorgement of the genitalia with arterial blood. Therefore applying a composition containing known vasodilating agents, including the instant compounds directly onto any area of the genital would have been reasonably

expected to be effective in causing vasodilatation and engorgement of the genitalia; and thereby treating female sexual dysfunction.

In addition, incorporating known topical pharmaceutical composition excipients such as cyclodextrin, gelatin, and hydroxypropyl methylcellulose such as hydroxypropyl methylcellulose 3000 (hydroxypropyl methylcellulose with a specific molecular weight) that are well known to be useful additives in forming topical compositions is considered within the skill of artisan.

Furthermroe, optimization of result effect parameters (e.g., the amount of ingredients such as hydroxymethylcellulose and misopriostol) is obvious as being within the skill of the artisan, absent evidence to the contrary.

Claims 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nahoum (US Patent 5, 773,457).

Nahoum teaches that both misoprostol and alprostadil are useful in treating female sexual dysfunction (See col. 9, lines 47-48; lines 53- col.10, line 1). Nahoum also teaches that misoprostol and alprostadil may be formulated into topical composition and that the topical female sexual dysfunction treatment composition may contain carboxy methylcellulose which is a known to be useful as gel-forming agent (See particularly col. 13, line 46-48).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to incorporate carboxymethyl cellulose and a second vasodilating

agent such as alprostadil into the misoprostol-containing female sexual dysfunction treating composition of Nahoum.

One of ordinary skill in the art would have been motivated to incorporate carboxymethyl cellulose into the misoprostol-containing female sexual dysfunction treating composition of Nahoum because carboxy methylcellulose is a known to be useful as gel-forming agent and incorporating such well-known gel-forming agent into the ocmpositoin of Nahoum in forming a gel composition is obvious as being within the purview of the skilled artisan, absent evidence to the contrary.

The motivation of incorporating a second vasodilating agent such as alprostadil, into the misoprostol-containing female sexual treating composition of Nahoum is provided by the cited prior art since combining two or more agents which are known to be useful as vasodilating agent individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Absent evidence to the contrary, no such evidence was seen to be present herein.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, there is no examples or

clinical studies presented for the evaluation of unexpected effectiveness of the instant invention. Therefore, no convincing and clear unexpected result over the cited prior art is seen.

Response to Arguments

Applicant's rebuttal arguments filed October 21, 2002 averring the cited prior art concerning H_3 agonists for treating sexual dysfunction have been fully considered but they are not persuasive. Please note that the new ground of rejection is not based on the teaching of Nahoum only. The rejection is based on the teachings of Lowery, Neal, Nahoum and Buyuktimkin et al. as primary references. These references teach the known vasoactive agents can modulate female sexual response, very much in the same way as modulation of male sexual response. Since misoprostol is a known vasoactive agent and can be used to treat male sexual dysfunction, employing such vasoactive agent to treat female sexual dysfunction would be reasonably expected to be effective, absent evidence to the contrary. Moreover, because of the vasactive nature of misoprostol, it is employed in Nahoum reference as an agent useful for treating female sexual dysfunction.

Applicant's rebuttal arguments filed October 21, 2002 averring the less irritation is observed in the instant invention have been considered, but are not found persuasive. Please note that the mucosal area (e.g., the inner mucosal surface of the urethra) is much more sensitive than the dermal layer. If the cited prior art teaches the intraurethral adminstration of misoprostol would not causing irritation problem, one of

ordinary skill in the art would reasonably expect the dermal would be much more easily tolerated, absent evidence to the contrary.

Applicant's rebuttal arguments filed October 21, 2002 averring examiner mistakenly asserts misoprostol and alprostadil being the same have been considered, but are not found persuasive. It is well-known that both agents are vasodilating agents and can be used in treating sexual dysfunction.

Applicant's rebuttal arguments filed October 21, 2002 averring the penetration properties of misoprostol and alprostadil have been considered but are not found persuasive. Please note that the claims do not expressly exclude any penetration enhancing agents to be incorporated in the topical misoprostol formulation. Therefore, incorporate a penetration enhancer, such as that described in Buyuktimkin et al., into the formulation of misoprostol in treating female sexual dysfunction would be reasonably expected to be useful.

Response to the Declaration by Mr. Fotinos

Fotinos' opinion statements in the Declaration, paragraph 4, filed January 15, 2002 that the pharmacological activity of topically applied misoprostol was substantially superior to other prostaglandins in particular, alprostadil in the treatment for female sexual dysfunction have been considered but are not found persuasive as to the nonobviousness of the instant claimed invention. The data demonstrates the effectiveness of misoprostol formulation, in absence of any organic solvent or penetration enhancer, to be more effective than that of prostaglandin E_1. As discussed

above, the claims are not expressly exclude any incorporation of penetration enhancer into the herein claimed composition. Therefore, possessing the teachings of the cited prior art, as a whole, one of ordinary skill in the art would still expect to employ misoprostol with/without alprostadil into a topical composition with penetration enhancer in a method of treating female sexual dysfunction, absent evidence to the contrary. No such evidence is present herein.

No clear and convincing unexpected result for the claimed invention is demonstrated in the declaration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

RUSSELL TRAVERS
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